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Clinical and Neuroradiological Findings in Classic Infantile and Late-Onset Globoid-Cell Leukodystrophy (Krabbe Disease)

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In the present study the clinical course and imaging of early and late-onset forms of Krabbe disease are analyzed. We report on 11 patients with a biochemical diagnosis of galactosyl ceramide β-galactoside deficiency. Two presented as the classic infantile form and died within the second year of life. In 9 children the first clinical signs, such as gait difficulties and visual failure, started after age 2 years. All these patients developed slow regression of motor and mental capacities, and most of them died within their first decade. In patients of both groups computed tomography (CT) and magnetic resonance imaging (MRI) were performed. In the late-onset form, hypodensities of the central white matter and pyramidal tracts were the leading radiological signs, whereas in the early-onset form, hyperdensities and cerebellar white matter lesions were also detected. From our results it becomes clear that variability of Krabbe disease refers not only to clinical manifestation but also to CT and MRI findings. Better knowledge of phenotypic and radiological diversity will help to understand the pathogenesis of the disease. © 1996 Wiley-Liss, Inc.

KEY WORDS: Krabbe disease, galactosyl ceramide β-galactosidase deficiency, magnetic resonance imaging, computed tomography, globoid-cell leukodystrophy

INTRODUCTION

Krabbe disease (KD) or globoid-cell leukodystrophy is a genetic degenerative disease of the central and peripheral nervous systems characterized by an abnormal breakdown and turnover of myelin. The biochemical diagnosis is based on findings of markedly reduced galactosyl ceramide β-galactosidase (GCG) activity in leukocytes or cultured fibroblasts [Suzuki and Suzuki, 1970]. GCG is a lysosomal enzyme (E.C. 3.2.1.46) required for the catabolism of β-galactocerebroside, a major component of the myelin sheath. Deficiency of this enzyme not only blocks the degradation of cerebroside, but also that of its deacylated derivative galactosylsphingosine (psychosine), which is known to be extremely toxic for oligodendrocytes [Svennerholm et al., 1980]. However, how much the increased psychosine concentration contributes to white-matter degeneration in Krabbe disease needs to be elucidated. Pathological examination of the brain shows a profound loss of oligondendroglia, a diffuse rarefication of white matter which may assume microcystic appearance, and astrogliosis. Globoid cells are multinucleated PAS positive elements of mesodermal origin, that contain inclusion bodies and are frequently noted as perivascular cuffs. According to Suzuki [1994], these cells represent a reaction of macrophages to accumulated galactocerebroside.

Based on age and clinical symptoms at onset, different forms of KD have been delineated [Hagberg, 1984]. In the infantile form, irritability, frequent crying, and increase of muscular tonus appear at age 3–6 months. Thereafter, opisthotonus, loss of tendineous reflexes, and visual failure become evident. Protein of the cerebrospinal fluid (CSF) is usually elevated, and nerve conduction velocity (NCV) is delayed. Death occurs within the second year.

In late-onset KD (LOKD), clinical manifestation does not begin before the second year of life [Hagberg, 1984]. Most of the reported LOKD patients had first symp-

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

Abbreviations: GCG, galactosyl ceramide β-galactosidase; KD, Krabbe disease; LOKD, late-onset Krabbe disease; NCV, nerve conduction velocity; CSF, cerebrospinal fluid.

toms before age 5 years or within the first decade [Hagberg, 1984; Kolodny et al., 1991; Loonen et al., 1985]. Clinical presentation occurred with signs of focal neurological damage: hemiparesis, cerebellar ataxia, and cortical blindness were the most frequent signs at onset of the disease. Progressive motor impairment leading to spastic tetraplegia was observed later during the clinical course [Loonen et al., 1985; Lyon et al., 1991]. First observations of LOKD in adult patients were made postmortem, and their diagnosis was based only on findings of characteristic neuropathology [Gullain et al., 1941]. Recently, enzymatic confirmation has been provided in cases of KD beginning later in childhood or in adulthood [Grewal et al., 1991; Verdru et al., 1991].

Krabbe leukodystrophy is an autosomal-recessive trait. The gene coding for GALC has been mapped in 14q24.3–q32.1 [Oehlman et al., 1993].

We report on the clinical and neuroradiologicl findings in 11 patients with Krabbe disease. The marked differences in clinical presentation and neuroimaging detected between the infantile and the late-onset types of the disease are discussed.

PATIENTS AND RESULTS

In this study 11 patients were included who had a marked deficiency of the enzyme galactosyl ceramide β-galactosidase in their fibroblasts. Symptoms and signs corresponded to KD of the early (2 cases) and late onset (9 cases) types. All children underwent extensive neuroradiological examination. In addition to brain CT scan, MRI examination was performed in 3 patients. Clinical and radiological data for patients with infantile and late-onset types are summarized in Tables I and II, respectively.

Infantile Krabbe Disease

Clinical findings. Two unrelated subjects, ages 8 and 6 months, were hospitalized for increasing irritability, unprovoked crying, and failure to thrive. Family medical history and pregnancy were unremarkable. On neurological examination, delay in psychomotor development was noted; the patients did not have head control, and showed poor visual response. There were generalized hypertonicity and brisk tendon reflexes, and active movements were rare. They both also exhibited startle-response to sudden stimuli and myoclonic jerks. Cerebrospinal spinal fluid (CSF) examination showed an elevated protein content (78 and 130 mg/dl, respectively). Motor nerve conduction velocity was slow (32 and 10 m/sec, respectively, on the median nerve; normal value, 44 m/sec). Both patients deteriorated rapidly into a decorticate posture and died before age 2 years after a complicated infectious episode.

Neuroradiological findings. CT scan (patient 1) documented bilateral circumscribed areas of slightly increased density within the centrum semiovale, probably corresponding to the corticospinal tracts (Fig. 1). MRI (patient 2) showed abnormally high signal intensity in the centrum semiovale on T2-W images, without involvement of the subcortical U-fibers (Fig. 2a). Increased signal was also noted in the brain stem, extending from the base of the pons to the midbrain as well as in the cerebellar white matter and the centers of the dentate nuclei. Low signal on T2-W images was observed in the thalami and to a small degree also within the dentate nuclei. There was no enhancement after administration of contrast medium.

Late-Onset Krabbe Disease

Clinical findings. Nine patients of Sicilian origin, including 2 sibs, presented with the late-onset form of Krabbe disease. Consanguinity of the parents was ascertained in 3 cases. Clinical data were published on 7 of these patients [Fiumara et al., 1990]. They were born at term after uncomplicated pregnancy and delivery. Initial development was regular in all patients, and first symptoms appeared at age 1½–5 years. Initial signs were spastic diplegia in 5 cases, visual difficulty in 2 cases, and paresis of the left upper limb in 1 case. Irritability and behavior changes appeared in some patients, but initially without involvement of mental performance.

Subsequently, progressive deterioration of motor capabilities was observed. The children became unable to stand or to maintain sitting position, and became bedridden with immobilizing spastic quadriplegia. Mental regression was also evident as they gradually lost speech and became unresponsive to environmental stimuli. All patients developed difficulty in chewing and swallowing and became emaciated. The course of the disease was 2–7 years, with mean age of death at

TABLE I. Main Clinical and Radiological Data in Infantile KD*

	Case 1	Case 2
Age-of-onset	2 months	3 months
Sex	Female	Female
Age examined	8 months	6 months
Clinical findings	Hypertonia, seizures	Hypertonia, seizures
Reduced NCV	+	+
Increased CSF protein	+	+
CT findings	Hyperdensity in CS	n.p.
MR findings	n.p.	$T_2\uparrow$ in CS, pons, CWM; $T_2\downarrow$ in T, ND
Age at death	15 months	8 months

*Age examined refers to age when clinical examination and radiological studies were performed. CS, centrum semiovale; T, thalamus; CWM, cerebellar white matter; ND, nucleus dentatus; NCV, nerve conduction velocity; $T_2\uparrow$, increased intensity on T2-W; $T_2\downarrow$, decreased intensity on T2-W; n.p., not performed.

TABLE II. Clinical and Radiological Findings in LOKD*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age of onset	4 years	25 months	3 years	2½ years	20 months	5 years	2 years	2 years	3 years
Sex	Female	Male	Female	Female	Female	Male	Female	Male	Female
Age examined	4½ years	3 years	6 years	4 years	3 years	5 years	2 years	4 years	3½ years
Clinical findings	Spastic diplegia	Spastic diplegia, behavior changes	Hemiparesis, ataxic gait	Seizures, diplegia, mental regression	Tetraparesis, mental regression	Ataxic gait, strabismus	Hemiparesis	Visual difficulty, mental regression	Spastic gait
Reduced NCV	–	+	n.p.	–	n.p.	+	–	–	–
CSF protein↑	+	+	n.p.	–	n.p.	n.p.	–	n.p.	n.p.
CT findings	Low density in FWM, PWM	Low density in OWM, CS	Low density in CS, IC	Low density in CS, IC; increased density in BG	Low density in FWM, PWM; hypodensity in pons	Low density in OWM	n.p.	Low density in PWM, OWM	n.p.
MR findings	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	T_2↑ in CS, IC T_2↓ in T	n.p.	T_2↓ in CS T_2↓ in T
Age at death	8 years	8 years	10 years	12 years	9 years	Alive	Alive	Alive	Alive

*Cases 2 and 3 are siblings. Cases 7 and 8 had follow-up (Table III). FWM, frontal deep white matter; PWM, parietal deep white matter; OWM, occipital deep white matter; CS, centrum semiovale; CC, corpus callosum; BG, basal ganglia; T, thalamus; IC, internal capsule; NCV, nerve conduction velocity; T_2↑, increased intensity on T2-W; T_2↓, decreased intensity on T2-W; n.p., not performed.

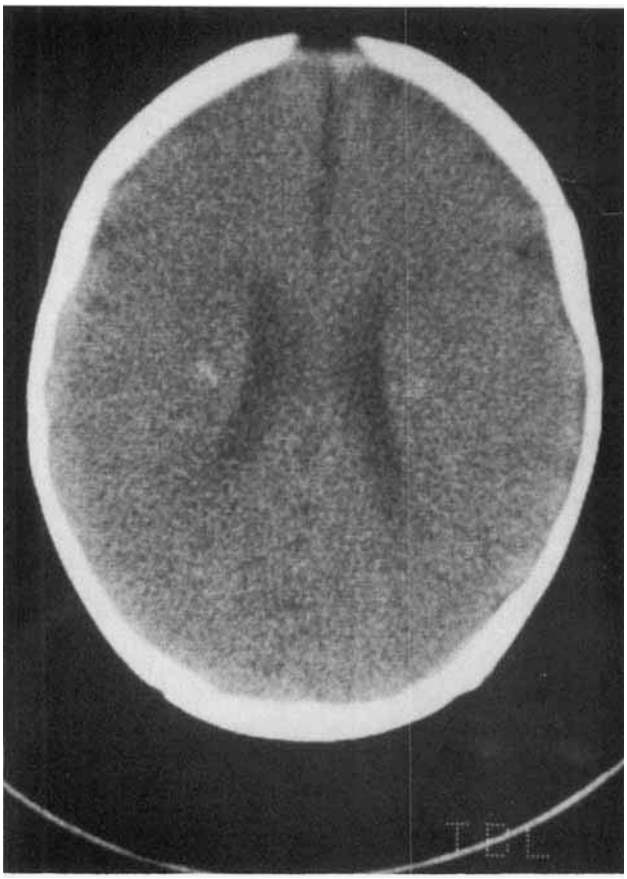

Fig. 1. Axial CT in KD, infantile form. Case 1. Eight-month-old child presenting with hypertonia and seizures. Bilateral circumscribed hyperdensities in central white matter.

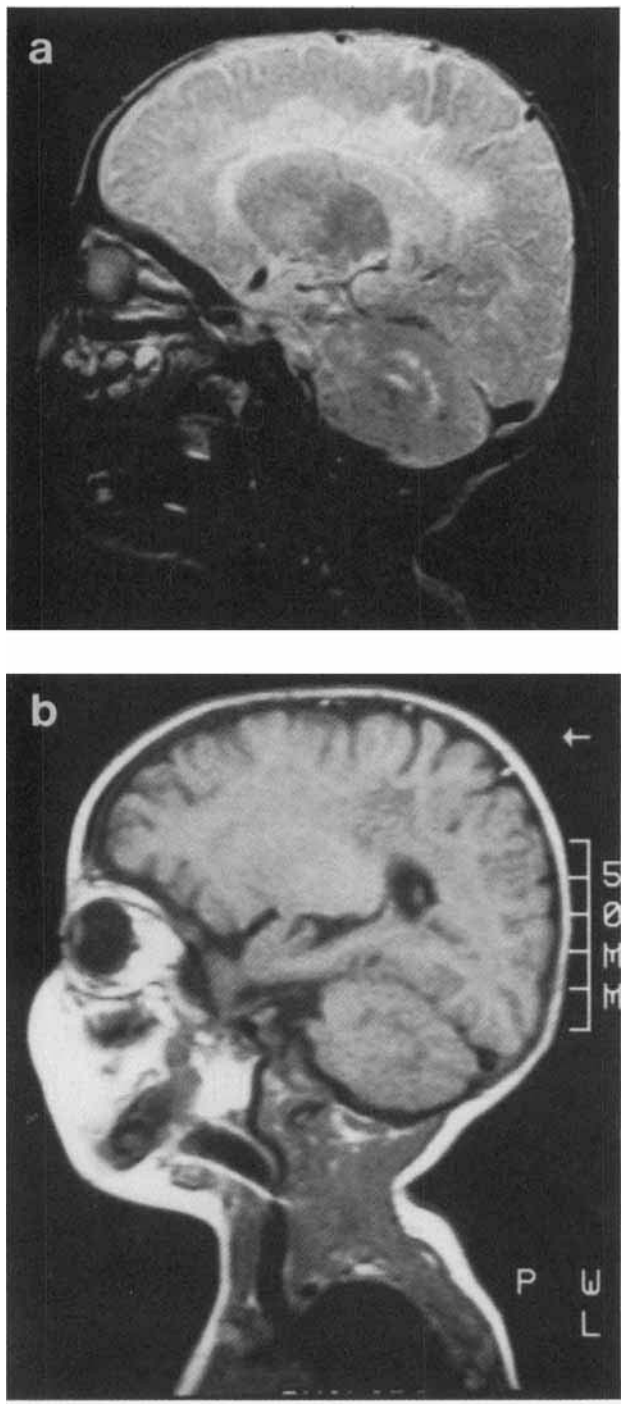

Fig. 2. MRI in KD, infantile form. Case 2. Six-month-old child presenting with developmental delay and severe generalized hypertonicity. **a:** Parasagittal MRI T2-W: Spinecho (SE) 2,000 msec; Repetition time (TR) 2,000 msec; Echo time (TE) 80 msec. Increased signal in centrum semiovale and cerebellar white matter. Decreased signal in thalamus and dentate nucleus. **b:** Parasagittal MRI T1-W (SE, TR, 520 msec; TE, 20 msec). Slightly decreased signal in centrum semiovale and cerebellar white matter.

9½ years. Four of the patients are still alive. In 2 of 4 patients who had CSF examination, an increase of protein was found. Only 2 out of 7 patients had shown a reduction of nerve conduction velocity.

Neuroradiological findings. All subjects underwent neuroradiological investigations. At the time of examination, age of the patients ranged from 2–6 years. Initial CT/MRI examination, performed 1–4 years after onset of symptoms, showed mild-to-moderate enlargement of the lateral ventricles in 6 of 9 cases. Slight atrophy of the cerebellum, brain stem, and cerebral cortex was found in 3 of these children, whereas 2 cases had no obvious atrophy on the initial imaging 2 years after onset of disease.

At least some degree of white-matter damage was present in all children, mostly affecting the parieto-occipital region of the centrum semiovale. In CT scan these lesions were represented by confluent or diffuse, mainly periventricular hypodensities (Fig. 3a), whereas T2-W MRI showed hyperintensities without involvement of the subcortical U-fibers (Fig. 4a).

There were additional circumscribed lesions within the internal capsules (Fig. 3b) and brain stem mainly affecting the pyramidal tracts, but also within the external capsules and corpus callosum. One patient showed slight signal drop within the cerebellar nuclei on T2-W imaging, without changes of the surrounding white matter (Fig. 4a). CT examination, in contrast to the usual white-matter hypodensities, showed a slight diffuse elevation of density within the basal ganglia in

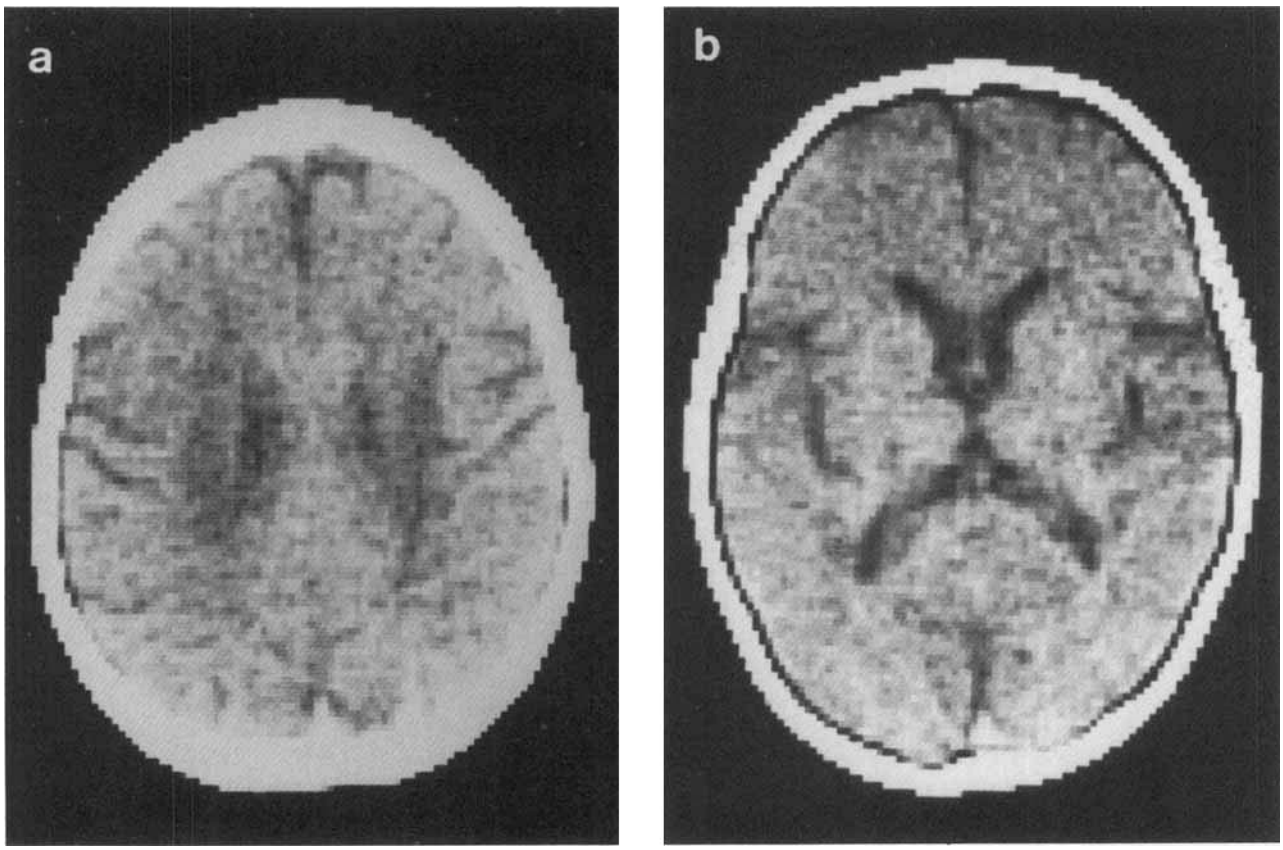

Fig. 3. CT in KD, late-onset form. Case 4. Four-year-old child with spastic tetraparesis. **a:** Axial CT at foramen of Monro. Slight hyperdensities of basal ganglia and decreased density of pyramidal tract within internal capsules. Slight ventricular enlargement. **b:** Axial CT at roof of lateral ventricle. Marked, central hypodensity of white matter. Subcortical U-fibers not affected.

one child 10 months after onset of symptoms, but no evidence of severe calcifications and no contrast enhancement (Fig. 3b). Follow-up studies with MRI were obtained in 2 patients, age 18 months and 8 years, respectively, after the initial examination (Table III). They document severe progression of the white-matter changes, with involvement of the subcortical U-fibers, corpus callosum, and external and internal capsules, and of the pyramidal tracts in the upper and lower parts of the brain stem. In these cases, progressive signal reduction of the thalami in T2-W imaging was also noted, as well as ventricular enlargement and atrophy of the cerebral cortex, brain stem, and cerebellum (Fig. 4b–d). In both cases, the clinical course had deteriorated to spastic tetraplegia.

DISCUSSION

According to the classification of Hagberg et al. [1969], the natural course of infantile KD comprises three clinical stages. The first is characterized by increasing muscular tone and irritability. In the following stages the patients progressively lose all their achieved abilities and gradually become opisthotonic.

We observed 2 patients with infantile KD (Table I). One child underwent MRI scan at age 6 months when she was in the second clinical stage of the disease: she presented a rigid posture with extension of the limbs and brisk tendon reflexes. Visual contact and social interaction were poor. On T2-W images, MRI demonstrated lowered intensity in thalami and dentate nuclei (Fig. 2a). Symmetric and mainly confluent lesions with increased T2-signal were seen within the cerebral and cerebellar white matter (Fig. 2b). Brain stem fiber tracts were also affected. These changes resemble other conditions of de- and dysmyelination progressing to generalized atrophy [Baram et al., 1986; Demaerel et al., 1990; Valk and van der Knaap, 1989].

High-density ares on CT examination are regarded as an early and rather specific finding of infantile KD [Cavanagh and Kendall, 1986; Kwan et al., 1984]. They involve both gray and white matter and may be detected in thalamus, cerebellum, brain stem, caudate nucleus, internal capsule, and corona radiata. In complementary MRI studies, such lesions have been described as having low signal on T2-W images [Baram et al., 1986], similar to our MRI findings within thalami and dentate nuclei. Mild signal elevation of the thalami on T1-W images has also been recorded [Finelli et al., 1994]. The nature of these lesions is still unclear: postmortem studies have demonstrated a high number of globoid cells and macrophages, as well as proliferating astrocytes in such areas [Percy et al., 1994].

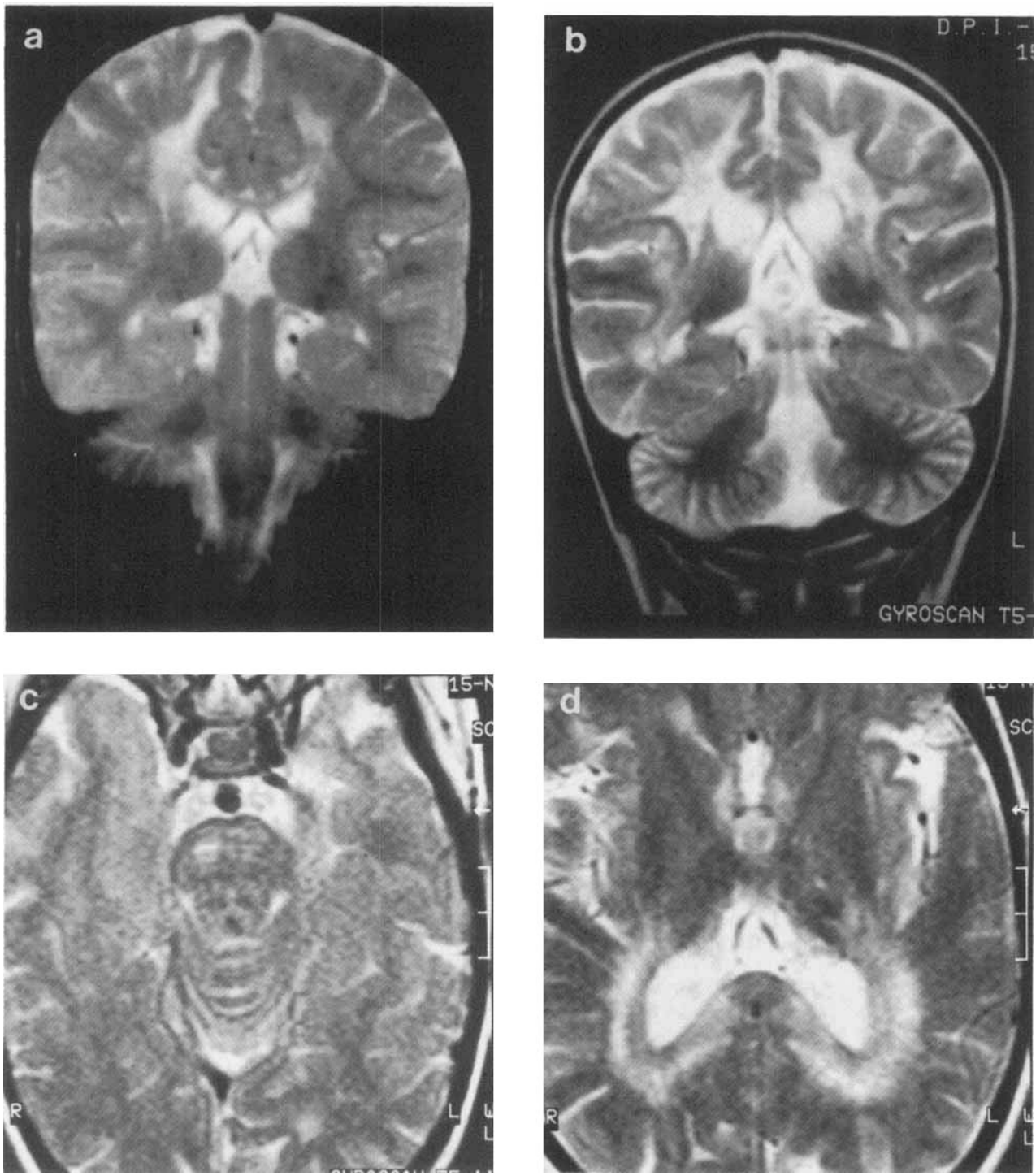

Fig. 4. MRI in KD, late-onset form. **a:** Case 7. Two-year-old child with left hemiplegia. Coronal MRI T2-W (SE, TR, 2,300 msec; TE, 120 msec) at level of aqueduct. Circumscribed and diffuse hyperintensities of supratentorial white matter, mainly centrum ovale. Subcortical U-fibers spared. Signal drop in dentate nucleus. **b–d:** Same patient 18 months later. She was opisthotonic, with hypertonic flexion of the arms, and extension of the legs and feet. b: Coronal MRI T2-W (SE, TR, 2,872 msec; TE, 120 msec) in similar position as Figure 4a. Progression of white matter hyperintensities with local involvement of U-fibers and ventricular enlargement. Additional cortical atrophy and hypointensity involving both thalami and dentate nuclei. c: Axial MRI T2W (SE, TR, 2,244 msec; TE, 120 msec) at level of upper pons. Circumscribed hyperintensities within pyramidal tract. d: Axial MRI, same parameters as c, at level of basal ganglia. Marked hyperintensity of occipital central white matter, sparing periventricular fibers to some degree. Circumscribed lesions within left internal and external capsules.

TABLE III. Clinical and Radiological Follow-Up in LOKD*

	Case 7	Case 8
Age	3½ years	12 years
Clinical features	Spastic tetraplegia, poor visual response, swallowing difficulty	Spastic tetraplegia, blindness, seizures, absent chewing and swallowing
MR findings	$T_2\uparrow$ in CS, CI, CC, pons, midbrain $T_2\downarrow$ in BG	$T_2\uparrow$ in CS, CI, CC, brain stem $T_2\downarrow$ in BG

*CS, centrum semiovale; CI, capsula interna; CC, corpus callosum; BG, basal ganglia; $T_2\uparrow$, increased intensity on T2-W; $T_2\downarrow$, decreased intensity on T2-W.

The CT of the second child with infantile KD showed increased density of the periventricular white matter in the area of the corticospinal tracts, resembling diffuse calcification (Fig. 1). Serum calcium levels were normal, and serological studies were negative for prenatal infections. In infantile KD, high-density areas may be observed early in the clinical course [Baram et al., 1986]. However, hyperdensity of white matter on CT examination is not a specific finding of KD, as it has been recorded in patients who had suffered from severe perinatal asphyxia [Cavanagh and Kendall, 1986], as well as in GM_2-gangliosidosis [Çaliskan et al., 1993]. White-matter and basal ganglia calcifications may also occur in several other conditions, including mineralizing microangiopathy, intrauterine infections, and hypoparathyroidism, but also in Krabbe disease. Confirmation of fine microcalcifications in the corona radiata has been provided at autopsy in 2 cases of infantile KD [Feanny et al., 1987; Percey et al., 1994].

Contrary to the almost uniform clinical picture of classic infantile form, a wide spectrum of clinical manifestations occurs in LOKD. It has been observed that under age 3 years, the disease has an acute onset and progresses rapidly. Conversely, patients with onset in childhood or in adulthood usually have a prolonged clinical course. They show rather preserved mental capabilities in contrast to severe motor and visual impairment [Arvidsson et al., 1995; Lyon et al., 1991; Phelps et al., 1991]. We observed 9 patients with LOKD (Table II). By age 1½–5 years the first symptoms appeared. All manifested severe signs of cortiospinal tract involvement, mainly spastic quadriparesis, increased muscle tone, and brisk deep tendon reflexes. All had profound mental deterioration. No differences in clinical manifestations were observed in 2 sibs.

Since late-onset globoid cell leukodystrophy is rare, neuroimaging studies have been reported only sporadically. The main findings consist of bilateral and highly confluent lesions of the deep white matter, in addition to ventricular enlargement and atrophy [Brownsworth et al., 1985; Comtuale et al., 1995; Kurokawa et al., 1987; Tada et al., 1992]. One patient has been reported who had a high-density lesion crossing the corpus callosum, resembling an infiltrating glioma [Epstein et al., 1991].

Neuroradiological investigations were performed in all our patients at varying times after onset of symptoms. In 2 patients the disease manifested with progressive visual problems and correlative CT-findings of low density in the parietooccipital regions. It has been mentioned that such clinical and radiological findings, usually observed in juvenile adrenoleukodystrophy, are not uncommon in LOKD as well [Kolodny et al., 1991]. However, in contrast to adrenoleukodystrophy, no enhancement after administration of contrast medium was found at the "active" border of the white-matter lesions, at least in our cases.

Two of 9 patients showed changes in deep gray matter, i.e., increased density areas in basal ganglia on CT scan, and complementary findings of reduced T2 signal on MRI. According to the reported data and our experience in LOKD, changes in the deep gray matter are usually detected in conjunction with a diffuse white-matter involvement [Comtuale et al., 1995; Kurokawa et al., 1987; Tada et al., 1992].

Serial MR observations were performed in 2 patients (Fig. 4a–d). In both of them, white-matter lesions were initially recognized in the occipital and parietal regions and then extended forward to the frontal and temporal white matter. This type of progression has been previously documented in one case of late-onset Krabbe disease [Tada et al., 1992]. Furthermore, degenerative changes of white matter expanded from the subependymal to the subcortical regions, also affecting the U-fibers in some areas. With progression of the disease, MR demonstrated increased signal in T2-W sequences within the splenium of corpus callosum, internal capsules, and the brain stem, mainly affecting the pyramidal tracts. Enlargement of the CSF spaces and widening of the cortical sulci became evident, indicating some additional gray matter atrophy. It is noteworthy that in these patients, age 3½–12 years, the progression of the lesions documented with MRI had reached a similar stage at age 18 months and 7 years, respectively, after onset of disease. This observation could be related to the clinical course that progressed rapidly in the younger patient, and suggests that in LOKD, after a rapid neurological deterioration, the disease seems to show a slow downhill course.

In both patients with infantile KD, changes of CT (patient 1) and T2-W images (patient 2), including cerebellar atrophy, appeared during the first year of life. The patients with LOKD showed slight-to-moderate cerebellar atrophy, but no additional changes in white matter were observed. Serial MR studies failed to show cerebellar white-matter involvement with the progression of the disease. In previous reports, cerebellar hyperintensities were seen in most patients with the infantile form [Baram et al., 1986; Choi et al, 1991; Farley et al., 1992]. They have not been found in LOKD;

however, there are only a few radiological [Brownsworth et al., 1985; Comtuale et al, 1995; Kurokawa et al., 1987; Tada et al., 1992; Thomas et al., 1984; Vanhanen et al., 1994] and neuropathological [Choi and Enzmann, 1993] reports on this form.

It has to be mentioned that in KD regional differences in white-matter exist, suggesting that some factors with different local distribution may play a role in the pathogenesis of the disease [Suzuki et al., 1994]. Studies on animal models have demonstrated that areas with more severe lesions correspond to regions of higher galactosylceramide turnover [Yamanaka et al., 1981]; however, reasons for the variability in distribution of white-matter lesions in different forms of the disease are unknown as yet.

According to the clinical presentation, neurological variants are known in both infantile and late-onset Krabbe disease [Kolodny et al., 1991], and morphological findings can be variable as well. As a matter of fact, it has been observed that in some patients with a prolonged clinical course, globoid cells could not be detected, and it has been proposed that they may degenerate and eventually disappear [Dunn et al., 1976; Gullotta et al., 1979; Suzuki, 1994].

It has been demonstrated that clinical heterogeneity in different forms of Krabbe disease is not related to the level of residual galactosyl ceramide β-galactosidase activity [Lyon et al., 1991]. Dunn et al. [1976] suggested that clinical variability may be explained by differences in the activation of enzyme systems that control the level of galactosylsphingosine.

We stress the importance of neuroimages for better evaluation of the wide clinical spectrum of KD. A better knowledge of clinical and radiological presentation in different types of the disease will be helpful in diagnostic procedure. Further clinical and neuroradiological studies, as well as postmortem biochemical analyses in patients with late-onset Krabbe disease, could be helpful in giving an insight into the pathogenesis of the disorder.

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